REMARKS/ARGUMENTS

Claims 56-58, 61, 63-66, 71-79, 81, 85, 86, 92-94, 97, 99, 164-191, 194-205, 207-209 are pending and examined. Claims 210-217 are added. Support for the newly added claims 210 and 212 is provided at, *e.g.*, page 28, lines 17-18 and page 35, lines 22-33 of the specification. Support for newly added claims 212-215 is provided at, *e.g.*, page 28, lines 13-15 and 17-19 of the specification. Support for newly added claims 216 and 217 is provided at, *e.g.*, page 28, lines 17-18 and 22 of the specification.

Applicants thank the Examiner for conducting an interview with the undersigned on April 7, 2008 at which the outstanding office action was discussed. Further aspects of the discussion will be referred to in the response that follows.

¶4. Applicant accepts the Examiner's priority date for purposes of responding to the office action. Applicant reserves the right to show an earlier date of invention should this become relevant in this or subsequent proceedings.

¶5. Claims 56-58, 61, 63, 64-66, 71-79, 81, 85-86, 92-94, 97, 99, 164-191, 194-205 and 207-209 stand rejected as allegedly obvious over Anderson and Becker in view of US Patent No. 5,593,846 ("the'846 patent"). Anderson and Becker are alleged to teach methods of diagnosing amyloid plaques in individuals using an antibody to Aβ. The '846 patent is alleged to teach that antibodies specific for residues 13-28 are useful for detecting of Aβ because they are not cross-reactive with the larger amyloid precursor protein. The '846 patent is also alleged to teach methods for *in vivo* diagnosis and treatment of Aβ related conditions. The Examiner takes the view that it would have been obvious to combine the 13-28 epitope specificity disclosed by Schenk in *in vivo* methods of diagnosis for the benefit of distinguishing between Aβ and APP. This rejection is respectfully traversed.

As discussed at the interview, the '846 patent does not disclose administration of the 266 antibody to a patient for purposes of a diagnosis or otherwise. Although the '846 patent

refers to *in vivo* and *in vitro* detection of Aβ, a careful reading of the patent reveals that these terms are consistently used to refer to detection of Aβ in body fluids and cell culture media respectively (see col. 6, lines 1-14; col. 8, lines 14-19; col. 10, lines 6-12; col. 10, lines 26-29 and col. 10, lines 58-67). Both *in vivo* and in vitro detection are performed using detection techniques, such as ELISA, Western blotting, radioimmunoassay and the like (col. 8, lines 34-36). The '846 patent does not proposed administering an antibody to a patient or discuss any means of detecting an antibody after administration to a patient (e.g., imaging). Although in other contexts, the *term in vitro* diagnosis might be used to refer to *in vivo* imaging and the like, the context in which this term is used in the Schenk patent leaves no doubt that the intended reference is to detection in isolated body fluids using assays such as ELISA, Western blotting or radioimmunoassay and the like. Thus, an artisan reading the '846 patent at the relevant time would not have viewed it as proposing using the 266 antibody for administration to a patient, nor found any rationale to encourage such use.

In the previous response, it was also pointed out that post-filing art indicates that the 266 antibody has little propensity to bind plaques compared with its ability to bind soluble Aβ, and that such characteristic would be undesirable for an antibody being used for diagnosis in a patient. As an initial matter, applicant notes that very recent unpublished results have indicated that the 266 antibody may in some instances show detectable binding to plaques, but observation of such binding depends on the source of plaques, type of plaques and how the 266 antibody is labeled. Thus, the underlying point remains that the 266 antibody is not and would not have been an antibody of choice for imaging plaques. Although the Examiner may be correct that such information was not known at the relevant priority date, it was nevertheless an inherent property of the antibody. Before the artisan went to the trouble of producing a chimeric or humanized version of 266 for in vivo diagnosis, the artisan would almost certainly have tested the mouse antibody for its capacity to bind to plaques. The artisan would have observed at best inferior performance of the 266 antibody and would likely have proceeded no further.

The Examiner also alleges that the ability of the 266 antibody to bind soluble Aβ would have motivated its use for diagnostic testing in a patient. Although the ability of 266 antibody to bind soluble Aβ was useful for the types of assays described in the '846 patent, such

as ELISA assays to detect soluble Aβ in body fluids removed from a patient or culture media, the '846 patent provides no indication that attempting to detect soluble Aβ in situ in body fluids would have been a feasible or useful means of diagnosing Alzheimer's disease. The characteristic pathology of Alzheimer's disease is insoluble Aβ in the form of plaques. A propensity for binding soluble Aβ would not have been seen as useful for binding this characteristic pathology.

Further, the purported combination of references in which a discussion of detecting soluble Aβ in bodily fluids removed from a patient is redeployed to render obvious a method of treating Alzheimer's disease also fails to take into account the lack of reasonable expectation of success in providing a treatment to a hitherto untreatable disease. Neither of the primary references provides any data to show that Alzheimer's disease can be treated or diagnosed by *in vivo* imaging. Becker is an entirely prophetic application. Moreover, this application has been abandoned in all jurisdictions suggesting that even the owners of the Becker application were not feeling optimistic of success (*see* the Inpadoc search report attached hereto). Anderson merely provides an experiment in which Aβ peptides are reported to stimulate tPA *in vitro*.

The lack of expectation that a treatment for Alzheimer's disease was on the horizon is illustrated by the following comments from third parties when the present inventor's work was first published.

> While the amyloid hypothesis has offered drug researchers a number of obvious targets and strategies, it also led to *the most surprising attempt to thwart AD.* In the late 1990's, long after his colleagues at Elan had tested their most promising compounds, Schenk suggested injecting a few mice with beta amyloid itself. His goal was to raise an antibody or other immune response against plaques. "No one thought it would work. Even after the experiment was done, the results weren't analyzed for a while," recalls Schenk.
>
> The results were stunning. The immunization slowed or preventing the development of beta-amyloid plaques in young mice and even wiped away preexisting ones in older mice. *The*

> *episode illustrates how one person's idea can change the direction of a company or a field.* "Dale was really brave," says John Trojanowski of the University of Pennsylvania School of Medicine in Philadelphia.
>
> *How does big pharma react when a disease-treating strategy such as the Elan vaccine comes out of the blue?*
>
> Travis, Science, 309, 731-734 (2005) (emphasis supplied) (cite no. 857, cited in Supplemental IDS submitted 07/19/2007).

Although these comments were made primarily with reference to active immunotherapy rather than passive immunotherapy as claimed, they illustrate more generally that the first demonstration of disease modification in an animal model by an immunotherapeutic approach was regarded as dramatic and surprising news that changed the direction of the field. It follows that those in the field did not assume that Alzheimer's disease could be successfully treated with 266 antibody therapy, simply based on the use of 266 to detect soluble Aβ in body fluids removed from a patient.

Numerous similar comments have been made by disinterested third parties after learning of the first publication of the present inventor's results.

> This is the first time that anyone has stopped the development of amyloid plaques in a mouse model of Alzheimer's.... This is a major step forward. If it does work, it would stand as one of the great scientific success stories of all time.
>
> Marcell Morrison-Bogorad of the National Institute on Aging in Science News Online 156, 2 (July 10, 1999), (cite no. 839, cited in Supplemental IDS submitted 07/19/2007).
>
> It's wild and amazing....Almost all scientists would have dismissed the immunization approach... because of the dogma that the so-called blood-brain barrier keeps circulating antibodies out of the brain.
>
> Sangram S. Sisodia, University of Chicago. Science News Online 156, 2 (July 10, 1999), (cite no. 839, cited in Supplemental IDS submitted 07/19/2007).

> Schenk surprised the Alzheimer's research community in June 1999 when he announced the vaccine worked to stop and even somewhat reverse the disease in mice. These mice were observed to perform better on memory tests.
>
> Free Press, July 23, 2001, (cite no. 840, cited in Supplemental IDS submitted 07/19/2007).
>
> The idea was revolutionary because most Alzheimer's experts believe that the inflammation provoked by amyloid plaques contributes to the destruction of brain cells. Many predicted that stirring up the immune system with a vaccine would only make the disease worse....Schenk's 1999 paper on the Elan vaccine created a sensation not least because the unexpected findings suggested that vaccines might be helpful in disorders where no one had thought of using them. His results have since been confirmed by other researchers.
>
> Washington Post, May 8, 2001, (cite no. 841, cited in Supplemental IDS submitted 07/19/2007)

Further, the inventor of the present application, Dr. Dale Schenk, was awarded the 2001 Potamkin Prize of the American Academy of Neurology (see the enclosed press release). This is an internationally recognized award for scientists who have made a significant contribution to the prevention or treatment of neurological disease. Roger Rosenberg, M.D., former president of the American Academy of Neurology, said that Dr. Schenk's research was recognized for the "quantum leap in thinking and implementation that it provides." Dr. Rosenberg added: "So important and unexpected are these findings that we awarded Dr. Schenk the Potamkin Prize as a solo award, recognition previously accorded only to Dr. Robert Terry and Dr. Stanley Prusiner" (both of whom subsequently won the Nobel Prize).

The above comments show that disinterested observers were not convinced of immunotherapy as a viable treatment of Alzheimer's disease until publication of the first results showing disease modification in an animal model in the present inventor's work in mid-1999. Absent a reasonable expectation of success of treating Alzheimer's disease, it was not obvious to combine the teachings of the cited references to arrive at the claimed invention.

Although the references cited by applicant showing surprise at the breakthrough nature of the present inventor's work do not specifically discuss the Anderson, Becker or Schenk references cited in the office action, it cannot reasonably be expected that evidence of this type (spontaneous comments by neutral experts unconnected with the prosecution of the application) would discuss the precise rejections later made by a patent examiner. The evidence is of value because it includes the unbiased opinions of experts working in the field at the relevant time and is free of the distortions of hindsight when the art is viewed for the first time only after acquiring knowledge that the claimed methods are in fact successful. Moreover, the references do indicate what it was about the present inventor's work that was regarded as dramatic, surprising and changing the direction of the field notwithstanding references such as Anderson, Becker and Schenk. That is, the present inventor's work represents the first demonstration of modification of Alzheimer's disease in an animal model.

As was discussed at the interview, whether the cited art provided a reasonable expectation of success is a different issue than whether the cited art references are themselves enabling. A prophetic reference describing a proposed method can work exactly as described (i.e., be enabling) but also be unpredictable because of the nature of the subject matter and because no data are provided to show that the method works. A reference that is itself unpredictable does not render future developments in the field any more predictable unless and until the source of unpredictability is removed. Thus, applicant's remarks concerning the lack of reasonable expectation of success do not require the Examiner to find prophetic references such as Anderson and Becker to lack enablement, but simply to consider what predictive value those references would have to the skilled person at the effective filing date of the application without any supportive data.

Instead of considering these references from the perspective of the skilled person not knowing whether the methods discussed in the references would be successful in treatment or diagnosis of Alzheimer's disease, the Examiner instead appears to be viewing the references from an artificial perspective in which it is presumed that the methods had worked and all unpredictability is removed. The source of this presumption is MPEP 2121, which provides that "when the reference relied on expressly anticipates or makes obvious *all of the elements of the*

claimed invention, the reference is presumed to be operable (emphasis supplied)." Such a presumption is inapplicable here because no single reference is cited as disclosing or rendering obvious all elements of the invention. More fundamentally, however, operability, which equates to enablement, is not the same as predictability for the reasons discussed above.

In light of this further explanation, the Examiner is requested to weigh again the disinterested remarks of those skilled in the art on the surprising nature of the first publication of immunotherapy of Alzheimer's disease, because the relevant inquiry is whether the success would have been predictable to the artisan as of the filing date. Surprise expressed by such artisans after the filing date is evidence that success was indeed not predictable as of the filing date.

Certain dependent claims are distinguished on additional grounds. In particular, claims directed to humanized or chimeric forms of the 266 antibody are further distinguished in that the cited art does not reference a hybridoma deposit or provide sequences of the 266 antibody. Humanized or chimeric antibodies are made by sequencing the cDNA encoding the variable domains of a mouse antibody, and then synthesizing a chimeric or humanized antibody based in part on the sequences of the mouse antibody. Without the provision of a deposited hybridoma or amino acid sequences of the variable domains of the 266 antibody, it would not have been a routine matter to produce a humanized or chimeric version thereof.

Claims reciting a human IgG1 isotype would not have been obvious for the reasons identified in the previous response. In brief, the cited art provided no reason to think that this isotype, which promotes interactions between an antibody and Fc receptors, would be advantageous for detection in a patient. To the contrary, the skilled person would likely have thought that effector functions were undesirable in view of the belief that Alzheimer's disease was at least in part an inflammatory disease. These concerns are expressed in an article in the Washington Post appearing shortly after the present inventor's work in clearing plaques by immunization with Aβ was first published.

> The idea was revolutionary because most Alzheimer's experts believe that the inflammation provoked by amyloid plaques contributes to the destruction of brain cells. Many predicted that

> stirring up the immune system with a vaccine would only make the disease worse. . .Schenk's 1999 papers on the Elan vaccine created a sensation not least because the unexpected findings suggested that vaccines might be helpful in disorders where no one had thought of using them. His results have since been confirmed by other researchers.
>
> Washington Post, May 8, 2001 (cite no. 841, cited in Supplemental IDS submitted 07/19/2007).

The belief that stirring up the immune system would only make the disease worse would have suggested that effector functions would be undesirable. Absent any indication that effector functions would be desirable for treatment or prophylaxis of Alzheimer's disease, it would not have been obvious to use a human IgG1 isotype.

Newly added claims 210 and 211 recite that multiple doses of antibody are added depending on when the antibody concentration in the patient has returned to baseline or a predetermined percentage of peak concentration. Such a regime is a typical treatment regime in which the goal is to maintain continual presence of antibody. By contrast, diagnosis of a disease would typically be performed only once, and even if it were performed more than once, there would be no reason that the timing of the second antibody administration be determined by decline of levels of the first administration to baseline or a predetermined level. Similar considerations apply to claims 212-217.

Claims 94, 164 and 209 recite that the antibody is administered as a sustained release composition. Such compositions are useful for maintaining a therapeutic concentration of antibody for an extended period. By contrast, in imaging methods, the goal is to have antibody present at a single point in time when an image is taken. Thus, there would be no purpose in using a sustained release composition for imaging in a patient.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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61265778 v1

Inpadoc International
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EP 613-007
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Basic Patent (No,Kind,Date): CA 2115900 AA 940823 <No. of Patents: 004>

PATENT FAMILY:
CANADA (CA)
Patent (No,Kind,Date): CA 2115900 AA 940823
PHARMACEUTICAL SCREENS AND ANTIBODIES (English; French)
Patent Assignee: LILLY CO ELI (US); ATHENA NEUROSCIENCES INC (US)
Author (Inventor): BECKER GERALD W (US); BREMS DAVID N (US); CHANEY MICHAEL O (US); MAY PATRICK (US); RYDEL RUSSELL E (US); SIMMONS LINDA K (US); TOMASELLI KEVIN J (US)
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Applic (No,Kind,Date): CA 2115900 A 940217
IPC: * C12P-021/08; C07K-015/28; A61K-049/00; G01N-033/577; G01N-033/543; G01N-033/566
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PHARMACEUTICAL SCREENS AND ANTIBODIES. (English; French; German)
Patent Assignee: LILLY CO ELI (US); ATHENA NEUROSCIENCES INC (US)
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IPC: * G01N-033/68; C07K-015/28
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PHARMACEUTICAL SCREENS AND ANTIBODIES. (English; French; German)
Patent Assignee: LILLY CO ELI (US); ATHENA NEUROSCIENCES INC (US)
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IPC: * G01N-033/68; C07K-015/28
CA Abstract No: * 121(17)195902T
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EP 613007	P	930222	EP AA	PRIORITY (PATENT APPLICATION) (PRIORITAET (PATENTANMELDUNG)) US 21609 A 930222
EP 613007	P	940218	EP AE	EP-APPLICATION (EUROPAEISCHE ANMELDUNG) EP 94301170 A 940218
EP 613007	P	940831	EP AK	DESIGNATED CONTRACTING STATES IN AN APPLICATION WITHOUT SEARCH REPORT (IN EINER ANMELDUNG OHNE RECHERCHENBERICHT BENANNTE VERTRAGSSTAATEN) AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
EP 613007	P	940831	EP A2	PUBLICATION OF APPLICATION WITHOUT SEARCH REPORT (VEROEFFENTLICHUNG DER ANMELDUNG OHNE RECHERCHENBERICHT)
EP 613007	P	940831	EP 17P	REQUEST FOR EXAMINATION FILED (PRUEFUNGSANTRAG GESTELLT) 940226
EP 613007	P	951025	EP AK	DESIGNATED CONTRACTING STATES IN A SEARCH REPORT (IN EINEM RECHERCHENBERICHT BENANNTE VERTRAGSSTAATEN) AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
EP 613007	P	951025	EP A3	SEPARATE PUBLICATION OF THE SEARCH REPORT (ART. 93) (GESONDERTE VEROEFFENTLICHUNG DES RECHERCHENBERICHTS (ART. 93))
EP 613007	P	980304	EP 18D	DEEMED TO BE WITHDRAWN (ALS ZURUECKGENOMMEN GELTEN) 970902

JAPAN (JP)
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PHARMACEUTICAL CLEANING AND ANTIBODY (English)
Patent Assignee: LILLY CO ELI; ATENA NIYUUROSAIENSUIZU INC
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